## REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

The recitation "fast-type" in claims 63-82 have been revised to read "fast-dissolving" corresponding to the wording of the other claims.

Accordingly, the rejection of claims 63-82 under 35 USC 112, second paragraph, is deemed to be overcome.

Claim 1 has been amended to specify the mean particle size of the micronized AS-3201 contained in the composition. This amendment is effected in reply to the Examiner's suggestion set forth in the sentence bridging pages 2-3.

Claim 1 has further been amended to specify the content of micronized AS-3201 contained in the pharmaceutical composition.

The foregoing amendments to claim 1 are supported in the specification at page 3, lines 3-4 and page 7, lines 21-24.

Lastly, all claims have been revised to remove the "tablet" terminology. The claimed composition is intended to cover any kind of composition such as tablets, capsules, granules, etc. While not believed to limit the former claims to a tablet, the "tablet" terminology has been removed from the claims, to ensure that the claims are not potentially argued by an infringer to be limited to a tablet. Thus, the claims as amended above are deemed to cover any pharmaceutical composition such as tablets, capsules, granules, powders, etc. Please see page 5, lines 2-5 of the specification.

Claims 1-20 and 61-82 were rejected under 35 USC 103 as being unpatentable over Negoro et al. in view of Bavitz et al. This ground of rejection is again respectfully traversed.

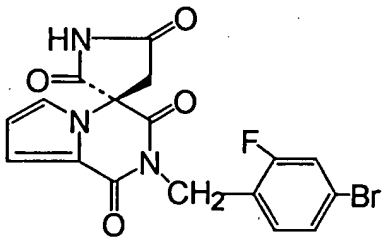
Firstly, the Examiner points out that the Applicant's argument is not persuasive since claim 1 does not recite particle sizes. As is mentioned above, in the foregoing amendment, the mean particle size of the active ingredient AS-3201 is specified in claim 1, and hence, this reason for rejection is obviated.

The Examiner further points out: that Example I and II of Bavitz et al. pointed out by the Applicant uses a sieve to sieve the mixture containing the already milled active agent and the sieve is in the micrometer range; that Bavitz et al.'s tablets contain an aldose reductase inhibitor with a dissolution amount of seventy-seven percent in ten minutes, which reads on the claimed dissolution rate of eighty percent within fifteen minutes; and further that unless a significant difference in dissolution is shown, it is not enough to support patentability of subject matter.

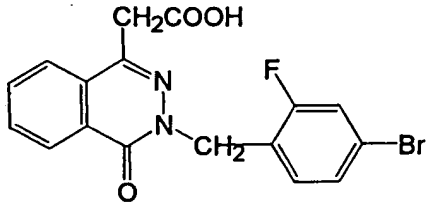
However, it should be noted that the active compound used in Bavitz et al. has a chemical structure significantly different from the chemical structure of AS-3201 of the present invention and owing to the difference of chemical structure, both compounds are significantly different in solubility which is independent from pharmacological property: i.e. aldose reductase inhibitory activity. So, even though the Bavitz et al. reference discloses uses of an aldose reductase inhibitor, there is no motivation for combining the Bavitz et al. reference with the Negoro et al. reference for preparing a fast-dissolving composition comprising a specifically micronized active compound aiming at improvement of the solubility of a hardly soluble compound. Besides, the milling procedure in Bavitz et al. is a mere standard procedure for preparing a pharmaceutical composition and is not for micronizing the compound in a specific mean particle size for improving solubility thereof.

These points are explained in more detail below.

(i) As is already pointed out in the response to the last Official Action, the phthalazineacetic acid compound used in Bavitz et al. is clearly different from the active ingredient of the present invention, AS-3201. The chemical structures are shown below.

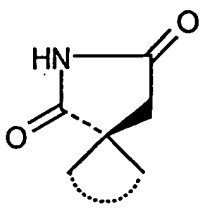



AS-3201




Phthalazineacetic acid compound

As is seen from the above chemical formulae, both compounds have a partial common structure in the halogenobenzyl substituent, but are different in the basic nucleus and are particularly different in another substituent, that is, the pyrrolidinedione having cyclic spiro-type structure in AS-3201 of the present invention of the following formula:




versus the acetic acid group of the formula: $-CH_2COOH$ of the corresponding substituent in Bavitz et al. Any person skilled in the art will readily understand that both compounds are entirely different from each other.

(ii) Owing to the difference in the chemical structure, the active compound of Bavitz et al. is also significantly different in solubility from AS-3201.

As is disclosed in Bavitz et al., Col. 3, Table I, for tablets containing 600 mg of active compound, the dissolution rate was 99% at 60 min. The test was carried out by the standard USP test method (wherein the test solution is 900 ml). Accordingly, the solubility (shown by the unit: μg/ml) of the active compound in Bavitz et al. is 99% x 600 mg/900 ml = 660 μg/ml, but on the other hand, the active compound AS-3201 of the present invention has a solubility of 47.6 μg/ml (measured by the inventors). Thus the active compound used in Bavitz et al. has a solubility of 14 times higher than the active compound AS-3201 of the present invention (660 μg/ml/47.6 μg/ml = 13.9).

(iii) In a pharmaceutical composition, for example, in the form of a tablet, of a hardly soluble active compound, there is usually a problem of low dissolution of the active compound from the tablet. Hence, it is important to improve the solubility of the active compound AS-3201 used in the present invention in order to prepare a pharmaceutical composition having an improved dissolving property. Thus, in view of extremely low solubility of the active compound of the present invention, ingenuity is required in order to increase the solubility of the active

compound AS-3201. On the contrary, because of the high solubility of the active compound in Bavitz et al., no ingenuity is required for providing a tablet of acceptable solubility, nor is there any motivation to design a tablet having increased solubility of the compound. It should be noted that the cited references do not teach the problem of the hardly soluble active compound AS-3201 of the present invention for preparing a pharmaceutical composition, particularly a tablet, much less the means for solution of the problem.

(iv) After extensive research, the present inventors have found that when the active compound AS-3201 is micronized in a certain particle size, it shows excellent solubility and further that the micronized AS-3201 having a specified mean particle size shall be contained in the desired composition in a specific ratio (0.5 - 25% by weight) on the basis of the total weight of the composition in order to show a high dissolution percentage of AS-3201 when compressed to prepare tablets.

On the other hand, in the tablets in Bavitz et al., the active compound is contained in 83-88% by weight as defined in claim 1, e.g. about 85.7% by weight in both of Example I and II (in Example 1, 300 mg of active compound is contained in one tablet of 350 mg, and in Example II, 600 mg of active compound is contained in one tablet of 700 mg).

Even when the active compound AS-3201 of the present invention is incorporated into a pharmaceutical composition in such a high ratio as in the Bavitz et al. composition, it does not produce the desired composition having a superior dissolving rate because most of the AS-3201 cannot be dissolved in the body liquid and hence is excreted from the body without being absorbed.

(v) Bavitz et al. disclose tablets containing an aldose reductase inhibitor as pointed out by the Examiner. The pharmacological activity has no direct relation on the dissolution properties of the compounds, which properties are relative to the physicochemical properties. In other words, even though some compounds have aldose reductase inhibitory activity, it cannot be assumed or implied that such compounds show the same or similar dissolution properties. Rather, such compounds will show much different solubilities, much like in the instant case of Bavitz et al. versus the instant invention.

Thus, even though another cited reference Negoro et al. (USP 5,258,382) disclose tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-yrrolidine derivatives having aldose reductase inhibitory activity, that U.S. patent is common to the instant U.S. patent application in the assignee: Dainippon Pharmaceutical Co., Ltd. There is no motivation to combine the Negoro et al. reference with the Bavitz et al. reference. Mere combination of Negoro et al. reference and Bavitz et al. reference does not teach or even suggest the specific claimed composition containing specifically micronized AS-3201 having superior fast-dissolving properties.

(vi) Moreover, Bavitz et al. disclose that the active compound is milled and further sieved, but those procedures are a mere standard procedure for preparing a pharmaceutical preparation, which are not the specific procedure for micronizing a compound having extremely low solubility to a specific particle size in order to improve the solubility, particularly to give fast-dissolving properties as claimed.

That is, the milling process of an active agent is known as one of many standard procedures in the pharmaceutical field for removing agglomerates of active agent and for obtaining a narrow particle size distribution. As explained in the response to the last Official Action, the sieving in Bavitz et al. is done for the purpose of sieving the agglomerates included in granules which are produced in the step of mixing and granulating of the active substance and pharmaceutical excipients or carriers. Therefore, the milling and further sieving steps are clearly distinguished from the micronization step in the present invention.

Again, the Applicant would emphasize that in view of such extremely low solubility of the active AS-3201 of the present invention, the present inventors have studied means for micronizing AS-3201 crystals suitable for preparing the desired pharmaceutical composition and have surprisingly found that when the AS-3201 crystals are micronized in a specific particle size, i.e. in a mean particle size of less than 20 μm, preferably less than 10 μm, the active AS-3201 can exhibit excellent solubility. As a result, the present inventors unexpectedly succeeded in preparation of an AS-3201 containing pharmaceutical composition which has extremely improved dissolving properties and superior bioavailability in comparison with a composition prepared by

using non-micronized AS-3201 crystals as is clear from comparison of the products of Examples and Reference Examples. See Experiments of the present description, particularly Fig. 1.

As is clear from the above explanation, the present invention is unexpectedly superior and clearly nonobvious from the cited references.

In view of the foregoing, it is respectfully submitted that the claims as amended are patentable over the prior art.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made**."

Accordingly, reconsideration and allowance is respectfully solicited.

Respectfully submitted,

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June 25, 2002

**Version with Markings to Show Changes Made**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re application of :

Mamoru OHASHI et al. : Docket No. 2000_0486A

Serial No. 09/529,715 : Group Art Unit 1616

Filed April 19, 2000 : Examiner S. Gollamudi

FAST-DISSOLVING PHARMACEUTICAL COMPOSITION

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## AMENDMENT

Assistant Commissioner for Patents,
Washington, D.C.

Sir:

Responsive to the Official Action dated August 21, 2001, the time for responding thereto being extended for two months in accordance with a petition for extension submitted concurrently herewith, please amend the above-identified application as follows:

## IN THE CLAIMS

Cancel without prejudice claims 21-60.

***Kindly amend the claims as follows:***

1. (Twice Amended) A fast-dissolving pharmaceutical composition comprising micronized (R)-2-(4-bromo-2-fluorobenzyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (hereinafter referred to as "AS-3201"), having a mean particle size of less than about 20 μm in a ratio of about 0.5% by weight to about 25% by weight of the total weight of the pharmaceutical composition,

wherein when ~~said composition is compressed into a tablet and~~ a dissolution percentage of AS-3201 from the ~~tablet~~ composition is measured according to the Paddle method, 50% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

5. **(Amended)** A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of about 0.5% by weight - 5% by weight, a diluent in a ratio of about 51% by weight - about 93.8% by weight, a disintegrator in a ratio of about 5% by weight - about 35% by weight, a binder in a ratio of about 0.5% by weight - about 5% by weight, and a lubricant in a ratio of about 0.2% by weight - about 4% by weight, relative to the total weight of the pharmaceutical composition,

wherein ~~when said composition is compressed into a tablet and~~ a dissolution percentage of AS-3201 from the ~~tablet~~ is measured according to the Paddle method, 50% or more of the AS-3201 in the ~~tablet~~ is dissolved within 15 minutes from the start of the method.

13. **(Amended)** A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of more than 5% by weight and less than about 25% by weight, a diluent in a ratio of about 16% by weight - about 84.3% by weight, a disintegrator in a ratio of about 10% by weight - about 50 % by weight, a binder in a ratio of about 0.5% by weight - about 5% by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4% by weight, relative to the total weight of the pharmaceutical composition,

wherein ~~when said composition is compressed into a tablet and~~ a dissolution percentage of AS-3201 from the ~~tablet~~ is measured according to the Paddle method, 50% or more of the AS-3201 in the ~~tablet~~ is dissolved within 15 minutes from the start of the method.

***Please add the following new claims:***

63. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 1, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method~~, 80% or more of the AS-3201 in the ~~tablet~~ is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

64. (~~New~~) The ~~fast-type dissolving~~ pharmaceutical composition according to claim 2, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the composition ~~tablet~~ is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

65. (~~New~~) The ~~fast-type dissolving~~ pharmaceutical composition according to claim 3, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the composition ~~tablet~~ is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

66. (~~New~~) The ~~fast-type dissolving~~ pharmaceutical composition according to claim 4, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the composition ~~tablet~~ is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

67. (~~New~~) The ~~fast-type dissolving~~ pharmaceutical composition according to claim 5, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the composition ~~tablet~~ is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

68. (~~New~~) The ~~fast-type dissolving~~ pharmaceutical composition according to claim 6, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the composition ~~tablet~~ is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

69. (~~New~~) The ~~fast-type dissolving~~ pharmaceutical composition according to claim 7, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-~~

~~3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

70. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 8, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method~~, 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

71. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 9, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

72. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 10, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

73. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 11, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

74. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 12, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

75. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 13, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

76. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 14, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method~~, 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

77. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 15, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method~~, 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

78. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 16, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method~~, 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

79. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 17, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method~~, 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) fast-dissolving

80. ~~(New)~~ The ~~fast-type dissolving~~ pharmaceutical composition according to claim 18, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-~~

~~3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) 81. ~~(New)~~ The ~~fast-type dissolving~~ fast-dissolving pharmaceutical composition according to claim 19, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.

(Amended) 82. ~~(New)~~ The ~~fast-type dissolving~~ fast-dissolving pharmaceutical composition according to claim 20, wherein ~~when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method,~~ 80% or more of the AS-3201 in the ~~tablet~~ composition is dissolved within 15 minutes from the start of the method.